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[Links](#)**NIJMEGEN BREAKAGE SYNDROME*****Alternative titles; symbols*****NBS****ATAXIA-TELANGIECTASIA VARIANT V1; AT-V1****MICROCEPHALY WITH NORMAL INTELLIGENCE, IMMUNODEFICIENCY, AND LYMPHORETICULAR MALIGNANCIES****SEEMANOVA SYNDROME II****NONSYNDROMAL MICROCEPHALY, AUTOSOMAL RECESSIVE, WITH NORMAL INTELLIGENCE****IMMUNODEFICIENCY, MICROCEPHALY, AND CHROMOSOMAL INSTABILITY**Gene map locus [8q21](#)**TEXT**

A number sign (#) is used with this entry because the disorder is caused by mutation in the NBS1 gene ([602667](#)).

Weemaes et al. (1981) described 2 sons of second-cousin parents who had microcephaly, stunted growth, mental retardation, cafe-au-lait spots, and immunodeficiency. Cytogenetic studies showed a typical form of chromosome instability with multiple rearrangements of chromosomes 7 and 14. A lower frequency of the same chromosome abnormalities was found in the father and 3 of the phenotypically normal sibs. Seemanova et al. (1985) described 9 patients in 6 families with a 'new' disorder characterized by low birthweight for dates, microcephaly with normal intelligence, receding mandibula, cellular and humoral immune defects, and increased risk of lymphoreticular malignancies. No evidence of chromosomal instability was found, but chromosome analysis was difficult because the rate of blastic transformation with phytohemagglutinin was low. Even sex ratio, consanguinity in 1 family and grandparental isonymy in a second, and the occurrence of 2 affected sibs in 3 families supported autosomal recessive inheritance. Bronchiectasis, pneumonia, otitis media, mastoiditis, and sinusitis occurred. Immunoglobulin levels were reduced. In 2 sibs, acute lymphoblastic leukemia developed at ages 9 years and 12 months, respectively. Generalized malignancies, apparently originating in the mediastinum and variously identified as malignant lymphogranuloma, acute undifferentiated

hemoblastoma and mediastinal blastoma (probably neuroblastoma) was the cause of death in several. The oldest surviving patient (of 4) was 12.5 years old. 🧠

Maraschio et al. (1986) described the case of a 31-year-old woman with primary amenorrhea, microcephaly and immunodeficiency. Her healthy parents were related as first cousins once removed. A younger sister, who also had primary amenorrhea, had died at age 20 years with a malignant lymphoma. Chromosome studies revealed a high proportion of metaphases with multiple chromosome aberrations. The same unbalanced translocation, t(8q;21q), was present in about 59% of metaphases. A few rearrangements involving chromosomes 7 and 14, similar to those described in patients with ataxia-telangiectasia (AT; 208900), were found. Sister-chromatid exchanges were not increased. 🧠

Teebi et al. (1987) reported a large inbred Arab kindred in which 8 individuals in 5 sibships had microcephaly and normal intelligence. Two died of acute lymphoreticular malignancy or bronchial pneumonia. Immunologic and chromosomal studies carried out in 3 affected living sibs yielded normal results. 🧠

It is now quite clear that at least 1 of the patients of Weemaes et al. (1981) and at least 2 of the patients of Seemanova et al. (1985) had the same basic defect; their cells failed to complement each other in cell fusion studies, using correction of radiosensitivity as the measure (Jaspers et al., 1988). There is at least one other syndrome of immunodeficiency, microcephaly, and chromosomal instability, which did show complementation with the other cases (Jaspers et al., 1988); the case of Conley et al. (1986) and 1 case of Sperling (1983) fell into this category. The patient of Sperling (1983) was further studied by Wegner et al. (1988). Jaspers et al. (1988) found that the disorder in all of these patients, which resembles ataxia-telangiectasia without the neurocutaneous manifestations, is indeed different from AT because fibroblasts from all cases show complementation with the 5 complementation groups of AT. Jaspers et al. (1988) performed complementation studies on fibroblast strains from 50 patients with either AT or NBS. Using the radioresistant DNA replication characteristic as a marker, they demonstrated 6 different genetic complementation groups, 2 of which, groups V1 and V2, involved patients with NBS. An individual with clinical symptoms of both AT and NBS was found in group V2, indicating that the 2 disorders are closely related. 🧠

Taalman et al. (1989) reported the findings in 5 families, 2 from the Netherlands and 3 from Czechoslovakia, containing a total of 8 patients. The basic karyotype in these patients was normal, but in a fifth or more of metaphases, rearrangements were found, preferentially involving chromosomes 7 and/or 14 at the sites 7p13, 7q34, and 14q11. The chromosomes of all 5 living patients were very sensitive to ionizing radiation. With ataxia-telangiectasia, NBS shares the occurrence of typical rearrangements of chromosomes 7 and 14, cellular and chromosomal hypersensitivity to x-irradiation, radioresistance of DNA replication, and immunodeficiency. However, NBS patients have microcephaly but neither ataxia nor telangiectasia, and they do not show elevation of serum alpha-fetoprotein, which is characteristic of AT. 🧠

Ataxia-telangiectasia variant-1 is the designation applied to the Nijmegen breakage

syndrome and AT variant-2, the designation for the Berlin breakage syndrome (600885). Stumm et al. (1995) noted that patients with these disorders share cytogenetic features with ataxia-telangiectasia (208900), such as spontaneous chromosomal instability, clonal occurrence of rearrangements involving, in particular, chromosomes 7 and 14, chromosomal and cellular hypersensitivity to irradiation, and 'radioresistant DNA synthesis.' However, despite the fact that these patients have neither ataxia nor telangiectasia, they historically have been categorized as AT variants. Clinically, they are characterized by pronounced microcephaly, microgenia, 'bird-like' facies, immunodeficiency, and normal serum levels of alpha-fetoprotein. The 2 syndromes can be distinguished from one another only by complementation analysis. 🧠

Chrzanowska et al. (1995) reported on 11 patients with Nijmegen breakage syndrome from 8 independent Polish families, with a total of 3 pairs of affected sibs. The clinical pattern included microcephaly, particular 'bird-like' face, growth retardation, and, in some cases, mild to moderate mental deficiency. Most of the patients had recurrent respiratory tract infections. One girl developed B-cell lymphoma. Chromosome studies showed structural aberrations with multiple rearrangements, preferentially involving chromosomes 7 and 14, in a proportion of metaphase in all individuals. Profound humoral and cellular immune defects were observed. Serum AFP levels were within normal range. Radioresistant DNA synthesis was strongly increased in all 8 patients who were studied from this point of view. 🧠

In 6 of the Polish families reported by Chrzanowska et al. (1995), Stumm et al. (1995) performed haplotype studies and sib-pair analysis and demonstrated lack of linkage to the 11q22-q23 region where the ataxia-telangiectasia locus maps. One of these families had been assigned to complementation group AT-V1 and a second to complementation group AT-V2 by cell-fusion studies. No complementation studies had been done in the other 4 families. 🧠

The clinical, immunologic, chromosomal, and cell-biologic findings in 42 patients in the NBS (Nijmegen breakage syndrome) Registry in Nijmegen were reviewed by van der Burgt et al. (1996). Although the immunologic, chromosomal, and cell-biologic findings resembled those in ataxia-telangiectasia, the clinical findings are quite different. The authors stated that NBS appears to be a separate entity not allelic with AT, as indicated by the fact that linkage studies exclude 11q22-q23, where the gene for ataxia-telangiectasia is located, as the site of the NBS gene. None of the patients had signs of cerebellar ataxia, apraxic eye movements, or other neurologic abnormalities except for twin girls described by Curry et al. (1989) who had clinical symptoms of both NBS and AT (see 607585.0014). Complementation studies assigned these cases to NBS complementation group V1. Subtle scleral telangiectasia was noted in 10 of 25 patients. The patients did not have raised serum AFP levels, as in ataxia-telangiectasia. Twelve patients varying in age from 1 to 22 years had developed lymphoma. One patient developed a glioma at the age of 12 years, 1 patient a medulloblastoma at 15 years, and 1 patient a rhabdomyosarcoma at 4 years. 🧠

Der Kaloustian et al. (1996) described a boy who in addition to typical manifestations had penoscrotal hypospadias. He had lymphopenia with low percentage of B and T

cells, absence of IgE, and low response to mitogen stimulation. At the age of 4 years he developed rhabdomyosarcoma. Cytogenetic study showed multiple chromatid and chromosome breaks, structural rearrangements involving mainly chromosomes 7 and 14, and different monosomies in 57 to 58% of cells. Nijmegen breakage syndrome was diagnosed, although hypospadias and a high percentage of monosomic cells led the authors to suggest he represented a specific variant of this syndrome. Der Kaloustian et al. (1996) suggested that the boy described by Woods et al. (1995) as a patient with Seckel syndrome might have the same variant of Nijmegen breakage syndrome. 💡

In the treatment of malignancies in patients with NBS, van der Burgt et al. (1996) stated that cytostatics are the first choice; however, radiomimetics (for example, bleomycin) should be avoided, and the chemotherapy doses should be reduced. Radiation therapy should be avoided, since x-irradiation can induce malignancies in NBS patients. 💡

NBS and the Berlin breakage syndrome (BBS; 600885) were considered separate entities on the basis of complementation studies which appeared to place them in separate complementation groups. These 2 so-called ataxia-telangiectasia variants are clinically indistinguishable, however. Saar et al. (1997) performed a whole-genome screen in 14 NBS/BBS families and localized the gene to a 1-cM interval on 8q21, between markers D8S271 and D8S270, with a peak lod score of 6.86 at D8S1811. This marker also showed strong allelic association to both Slavic NBS and German BBS patients, suggesting the existence of one major mutation of Slavic origin. The authors stated that since the same allele is seen in both complementation groups, genetic homogeneity of NBS/BBS can be considered as proved. Matsuura et al. (1997) used microcell-mediated chromosome transfer followed by complementation assays based on radiosensitivity to demonstrate that only chromosome 8 complements the sensitivity to ionizing radiation in NBS cell lines. In complementation assays performed after the transfer of a reduced chromosome, merely the long arm of chromosome 8 was sufficient for restoring the defect. The results supported the suggestion that NBS is a homogeneous disorder and that the gene for NBS is located at 8q21-q24. 💡

(Some of the patients studied by Saar et al. (1997) were Germans in whom the Berlin breakage syndrome had been described and others were Slavic patients in whom the Seemanova syndrome (a synonym for NBS) had been described. Saar et al. (1997) noted that it would be interesting to investigate whether Dutch patients also showed an allelic association at D8S1811, similar to what they had found in Slavic and German patients. In the first half of the 17th century, after the battle of Weissenberg in the Thirty Years War, a considerable number of Bohemian Protestants emigrated to the Netherlands from an area presently part of Poland and the Czech Republic. A major NBS mutation may have found its way to the Netherlands by migration.) 💡

Tupler et al. (1997) provided the first report of an Italian case of Nijmegen breakage syndrome. The proband was an immunodeficient, microcephalic, 11-year-old boy with a 'bird-like' face. He developed a T-cell-rich B-cell lymphoma. Spontaneous chromosomal instability was detected in T- and B-lymphocytes and in fibroblasts; chromosomes 7 and 14 were only sporadically involved in the rearrangements and no clonal abnormality was present. The patient appeared to be sensitive both to ionizing

radiation and to bleomycin, although his sensitivity did not reach the level of ataxia-telangiectasia reference cells. Although the clinical evaluation suggested to Tupler et al. (1997) a diagnosis of NBS, differences in the cytogenetic and cell-biologic data suggested that the patient might have an allelic form of the disorder. 💡

Stumm et al. (1997) found noncomplementation of radiation-induced chromosome aberrations in heterodikaryons between ataxia-telangiectasia and ataxia-telangiectasia variant cells. They suggested that the results of noncomplementation in AT/AT-V cell hybrids could be explained best by genes whose products contribute to a multisubunit protein involved in the damage response of radiation-induced chromosome aberrations. The data supported the assumption that the AT-V disorders represent a homogeneous genetic trait. 💡

In a geographically diverse group of NBS patients, Cerosaletti et al. (1998) reported linkage to 8q21 in 6 of 7 families, with a maximum lod score of 3.58. Significant linkage disequilibrium was detected for 8 of 13 markers tested in the 8q21 region, including D8S1811. To localize the gene for NBS further, they generated a radiation hybrid map of markers at 8q21 and constructed haplotypes based on this map. Examination of disease haplotypes segregating in 11 NBS pedigrees revealed recombination events that placed the NBS gene between D8S1757 and D8S270. A common founder haplotype was present in 15 of 18 disease chromosomes from 9 of 11 NBS families. Inferred (ancestral) recombination events involving this common haplotype suggested that NBS can be localized further, to an interval flanked by markers D8S273 and D8S88. 💡

Varon et al. (1998) and Carney et al. (1998) isolated the gene responsible for the Nijmegen breakage syndrome. Varon et al. (1998) isolated the gene by positional cloning and named it nibrin, while Carney et al. (1998) isolated the gene by biochemical analysis of the protein components of the MRE11 (600814)/RAD50 (604040) complex, and named it p95. Varon et al. (1998) identified mutations in the nibrin/p95 gene in patients with NBS. 💡

## SEE ALSO

Jaspers et al. (1988)

## REFERENCES

1. Carney, J. P.; Maser, R. S.; Olivares, H.; Davis, E. M.; Le Beau, M.; Yates, J. R., III; Hays, L.; Morgan, W. F.; Petrini, J. H. J. :

The hMre11/hRad50 protein complex and Nijmegen breakage syndrome: linkage of double-strand break repair to the cellular DNA damage response. *Cell* 93: 477-486, 1998.

PubMed ID : 9590181

*May 1*

2. Cerosaletti, K. M.; Lange, E.; Stringham, H. M.; Weemaes, C. M. R.; Smeets, D.; Solder, B.; Belohradsky, B. H.; Taylor, A. M. R.; Karnes, P.; Elliott, A.; Komatsu, K.; Gatti, R. A.; Boehnke, M.; Concannon, P. :

Fine localization of the Nijmegen breakage syndrome gene to 8q21: evidence for a common founder haplotype. *Am. J. Hum. Genet.* 63: 125-134, 1998.  
PubMed ID : [9634525](#)

3. Chrzanowska, K. H.; Kleijer, W. J.; Krajewska-Walasek, M.; Bialecka, M.; Gutkowska, A.; Goryluk-Kozakiewicz, B.; Michalkiewicz, J.; Stachowski, J.; Gregorek, H.; Lyson-Wojciechowska, G.; Janowicz, W.; Jozwiak, S. :

Eleven Polish patients with microcephaly, immunodeficiency and chromosomal instability: the Nijmegen breakage syndrome. *Am. J. Med. Genet.* 57: 462-471, 1995.

PubMed ID : [7545870](#)

4. Conley, M. E.; Spinner, M. B.; Emanuel, B. S.; Nowell, P. C.; Nichols, W. W. :  
A chromosome breakage syndrome with profound immunodeficiency. *Blood* 67: 1251-1256, 1986.

PubMed ID : [2421804](#)

5. Curry, C. J. R.; Tsai, J.; Hutchinson, H. T.; Jaspers, N. G. J.; Wara, D.; Gatti, R. A. :  
AT(Fresno): a phenotype linking ataxia-telangiectasia with the Nijmegen breakage syndrome. *Am. J. Hum. Genet.* 45: 270-275, 1989.

PubMed ID : [2491181](#)

6. Der Kaloustian, V. M.; Kleijer, W.; Booth, A.; Auerbach, A. D.; Mazer, B.; Elliott, A. M.; Abish, S.; Usher, R.; Watters, G.; Vekemans, M.; Eydoux, P. :

Possible new variant of Nijmegen breakage syndrome. *Am. J. Med. Genet.* 65: 21-26, 1996.

PubMed ID : [8914736](#)

7. Jaspers, N. G. J.; Gatti, R. A.; Baan, C.; Linssen, P. C. M. L.; Bootsma, D. :  
Genetic complementation analysis of ataxia telangiectasia and Nijmegen breakage syndrome: a survey of 50 patients. *Cytogenet. Cell Genet.* 49: 259-263, 1988.

PubMed ID : [3248383](#)

8. Jaspers, N. G. J.; Taalman, R. D. F. M.; Baan, C. :  
Patients with an inherited syndrome characterized by immunodeficiency, microcephaly, and chromosomal instability: genetic relationship to ataxia telangiectasia. *Am. J. Hum. Genet.* 42: 66-73, 1988.

PubMed ID : [3337113](#)

9. Maraschio, P.; Peretti, D.; Lambiase, S.; Lo Curto, F.; Caufin, D.; Gargantini, L.; Minoli, L.; Zuffardi, O. :

A new chromosome instability disorder. *Clin. Genet.* 30: 353-365, 1986.

PubMed ID : [3802554](#)

10. Matsuura, S.; Weemaes, C.; Smeets, D.; Takami, H.; Kondo, N.; Sakamoto, S.; Yano, N.; Nakamura, A.; Tauchi, H.; Endo, S.; Oshimura, M.; Komatsu, K. :

Genetic mapping using microcell-mediated chromosome transfer suggests a locus for Nijmegen breakage syndrome at chromosome 8q21-24. *Am. J. Hum. Genet.* 60: 1487-1494, 1997.

PubMed ID : [9199571](#)

11. Saar, K.; Chrzanowska, K. H.; Stumm, M.; Jung, M.; Nurnberg, G.; Wienker, T. F.; Seemanova, E.; Wegner, R.-D.; Reis, A.; Sperling, K. :

**The gene for the ataxia-telangiectasia variant, Nijmegen breakage syndrome, maps to a 1-cM interval on chromosome 8q21.** *Am. J. Hum. Genet.* 60: 605-610, 1997.

PubMed ID : [9042920](#)

12. Seemanova, E.; Passarge, E.; Beneskova, D.; Houstek, J.; Kasal, P.; Sevcikova, M. :  
**Familial microcephaly with normal intelligence, immunodeficiency, and risk of lymphoreticular malignancies: a new autosomal recessive disorder.** *Am. J. Med. Genet.* 20: 639-648, 1985.

PubMed ID : [3857858](#)

13. Sperling, K. :

**Analisi dell' eterogeneita nell'uomo.** *Prospettive Pediat.* 49: 53-66, 1983.

14. Stumm, M.; Gatti, R. A.; Reis, A.; Udar, N.; Chrzanowska, K.; Seemanova, E.; Sperling, K.; Wegner, R.-D. :

**The ataxia-telangiectasia-variant genes 1 and 2 are distinct from the ataxia-telangiectasia gene on chromosome 11q23.1.** (Letter) *Am. J. Hum. Genet.* 57: 960-962, 1995.

PubMed ID : [7573059](#)

15. Stumm, M.; Sperling, K.; Wegner, R.-D. :

**Noncomplementation of radiation-induced chromosome aberrations in ataxia-telangiectasia/ataxia-telangiectasia-variant heterodikaryons.** (Letter) *Am. J. Hum. Genet.* 60: 1246-1251, 1997.

PubMed ID : [9150175](#)

16. Taalman, R. D. F. M.; Hustinx, T. W. J.; Weemaes, C. M. R.; Seemanova, E.; Schmidt, A.; Passarge, E.; Scheres, J. M. J. C. :

**Further delineation of the Nijmegen breakage syndrome.** *Am. J. Med. Genet.* 32: 425-431, 1989.

PubMed ID : [2786340](#)

17. Teebi, A. S.; Al-Awadi, S. A.; White, A. G. :

**Autosomal recessive nonsyndromal microcephaly with normal intelligence.** *Am. J. Med. Genet.* 26: 355-359, 1987.

PubMed ID : [3812587](#)

18. Tupler, R.; Marseglia, G. L.; Stefanini, M.; Prosperi, E.; Chessa, L.; Nardo, T.; Marchi, A.; Maraschio, P. :

**A variant of the Nijmegen breakage syndrome with unusual cytogenetic features and intermediate cellular radiosensitivity.** *J. Med. Genet.* 34: 196-202, 1997.

PubMed ID : [9132489](#)

19. van der Burgt, I.; Chrzanowska, K. H.; Smeets, D.; Weemaes, C. :

**Nijmegen breakage syndrome.** *J. Med. Genet.* 33: 153-156, 1996.  
PubMed ID : [8929954](#)

20. Varon, R.; Vissinga, C.; Platzer, M.; Cerosaletti, K. M.; Chrzanowska, K. H.; Saar, K.; Beckmann, G.; Seemanova, E.; Cooper, P. R.; Nowak, N. J.; Stumm, M.; Weemaes, C. M. R.; Gatti, R. A.; Wilson, R. K.; Digweed, M.; Rosenthal, A.; Sperling, K.; Concannon, P.; Reis, A. :

**Nibrin, a novel DNA double-strand break repair protein, is mutated in Nijmegen breakage syndrome.** *Cell* 93: 467-476, 1998.  
PubMed ID : [9590180](#)

21. Weemaes, C. M. R.; Hustinx, T. W. J.; Scheres, J. M. J. C.; van Munster, P. J. J.; Bakkeren, J. A. J. M.; Taalman, R. D. F. M. :

**A new chromosomal instability disorder: the Nijmegen breakage syndrome.** *Acta Paediat. Scand.* 70: 557-564, 1981.  
PubMed ID : [7315300](#)

22. Wegner, R.-D.; Metzger, M.; Hanefeld, F.; Jaspers, N. G. J.; Baan, C.; Magdorf, K.; Kunze, J.; Sperling, K. :

**A new chromosomal instability disorder confirmed by complementation studies.** *Clin. Genet.* 33: 20-32, 1988.  
PubMed ID : [3277755](#)

23. Woods, C. G.; Leversha, M.; Rogers, J. G. :

**Severe intrauterine growth retardation with increased mitomycin C sensitivity: a further chromosome breakage syndrome.** *J. Med. Genet.* 32: 301-305, 1995.  
PubMed ID : [7643362](#)

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